T he bulletins from the nation’s therapeutic frontiers continue to read like the casualty reports from a lost war. At least once or twice a year, yet another pharmaceutical company or regulatory agency or biomedical journal releases yet another melancholic communiqué on the terrible effects of a drug that previously had been thought to be the greatest advance in medicine since aspirin or penicillin. We have had the demise of isotropic drugs for heart failure, of NEP-ACE inhibitors and COX-2 inhibitors, to mention a few of the more spectacular pieces of bad news. However, none could have been more surprising, and impacted more people, than the story of hormone replacement therapy (HRT). Menopausal symptoms can be grim, and it made perfect sense to replace the hormonal deficit with exogenous hormones, estrogen and progestin. The enthusiasm for HRT was greatly enhanced by the results of observational studies, which suggested that either estrogen alone or in combination with progestin seemed to improve many measures of cardiac and vascular health, including serum lipids and endothelial function, not to mention the prevention of osteoporosis and its damaging clinical consequences. There was also the tantalizing evidence that these agents slowed the decline in cognitive function and might help prevent Alzheimer disease. Because of all of the perceived benefits, it is no great surprise that by the mid-1990s HRT was the most frequently prescribed drug in the United States, in spite of some lingering worries about breast and endometrial cancer. The promise of cardiovascular protection. One of these agents is drosperone (DRSP), a novel progestin, that has been developed, in combination with 17-β-estradiol (E2), for use in postmenopausal women as HRT. DRSP is particularly interesting, and promising, because it is also an aldosterone antagonist.

The potential benefits of such a dual progestin and aldosterone antagonist action are great. A small study has shown that DRSP/E2 had an additive effect on lowering blood pressure (BP) in hypertensive postmenopausal women taking enalapril. However, the long-term advantage of such a progestin and aldosterone antagonist may extend beyond some modest BP-lowering effect. Activation of the renin-angiotensin-aldosterone system is now well-known to be a major mechanism of damage to the myocardium and vasculature. Most of the evidence for this is based on studies of angiotensin II, but more recent reports have also implicated aldosterone, independent of angiotensin II, in the pathogenesis of some types of progressive cardiovascular and renal disease. Aldosterone, besides its primary physiologic action of enhancing sodium and water reabsorption and potassium excretion by the kidney, also has bad effects such as the promotion of vascular inflammation and fibroblast collagen synthesis, vascular smooth muscle cell hypertrophy, an increase in free radical production, and impairment of endothelial function by reducing nitric oxide synthesis. This more sophisticated understanding of aldosterone actions has led to a new interest in aldosterone antagonists beyond their traditional use as potassium-sparing diuretics. In patients with chronic congestive heart failure aldosterone antagonists, such as spironolactone and epleronone, increase nitric oxide bioactivity, improve endothelial vasodilator dysfunction, reduce vascular collagen turnover, improve heart rate variability, and improve diastolic dysfunction. They also reduce vascular injury in hypertension and reduce proteinuria in patients with chronic renal disease. The clinical utility of these concepts was shown in two important clinical trials of aldosterone antagonists in the management of patients with congestive heart failure. In the first, Randomized Aldactone Evaluation Study (RALES), spironolactone given to patients with severe heart failure reduced mortality, the frequency of hospitalization for worsening heart failure, and improved symptoms. Then, in Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

From the Mount Sinai School of Medicine, New York, New York.


From the Mount Sinai School of Medicine, New York, New York, and the V.A. Medical Center, Bronx, New York.

Address correspondence and reprint requests to Dr. Clive Rosendorff, Medicine (111), V.A. Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468; e-mail: clive.rosendorff@med.va.gov

© 2005 by the American Journal of Hypertension, Ltd. Published by Elsevier Inc.
(EPHESUS),13 eplerenone also reduced overall mortality and also death from cardiovascular causes or hospitalization for cardiovascular events, in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

A concern in all of these studies has been the theoretical potential for serious hyperkalemia in patients treated with aldosterone antagonists, especially when prescribed together with angiotensin-converting enzyme (ACE) inhibitors. In RALES, serious hyperkalemia, defined as a serum potassium concentration of at least 6.0 mEq/L, occurred in only 10 patients in the placebo group (1%) and 14 patients in the spironolactone group (2%); this difference was not statistically significant. The EPHESUS investigators reported that at 1 year potassium levels increased in both the placebo and eplerenone groups (by 0.2 and 0.3 mEq/L, respectively, P < .001). Serious hyperkalemia, again defined as a serum potassium concentration of 6 mEq/L or greater, occurred in 5.5% of patients in the eplerenone group and 3.9% in the placebo group (P = .002). An additional risk factor for serious hyperkalemia was renal insufficiency. Among patients with a baseline creatinine clearance of less than 50 mL/min, the incidence of serious hyperkalemia was 10.1% in the epleronone group and 5.9% in the placebo group (P = .006).

It was inevitable, therefore, that the safety issue of hyperkalemia should be addressed for other spironolactone analogues, and in this issue Preston et al14 report just such a study for the DRSP/E2 combination. This was a multicenter trial of DRSP/E2 versus placebo in postmenopausal women with hypertension aged 45 to 70 years with or without type 2 diabetes mellitus, and all on an ACE inhibitor or an angiotensin II receptor antagonist (ARB). The end points were changes from the baseline in BP and the number (%) of subjects who developed hyperkalemia (here defined as a serum potassium concentration of ≥5.5 mEq/L). There were 82 subjects with, and 148 without, diabetes, randomized to DRSP 3 mg/E2 1 mg/d, or placebo, for 28 days. The nondiabetic group also received ibuprofen 400 mg three times a day for 5 days during treatment days 10 to 14 to potentiate any tendency to hyperkalemia.

The investigators state that the incidence of hyperkalemia in the DRSP/E2 and placebo groups was 7.3% and 2.6%, respectively, and this difference was not statistically significant. In the diabetic group the numbers were 7.9% and 4.5%, and in the nondiabetic subgroup, 6.9% and 1.4%, all with nonsignificant values for the difference between DRSP/E2 and control. Although the mean serum potassium values throughout the study in the DRSP/E2 group were consistently higher than in the placebo-treated subjects, the change of serum potassium from baseline values showed a small and statistically significant, “but not clinically significant,” difference in the means between the DRSP/E2 and placebo groups only on days 12, 15, and 20, but not on the other days on which potassium was measured. Baseline systolic/diastolic BP was reduced by 8.6/5.8 mm Hg on DRSP/E2 versus 3.7/2.9 mm Hg on placebo, a statistically significant difference.

There is good news and bad news from this study. The good news is that the hormone combination caused a substantial lowering of the BP. A decrease in BP of 8.6/5.8 mm Hg is impressive, and is bound to have some very positive public health implications for an older, postmenopausal, cohort of women, a large proportion of whom have or will develop systolic hypertension. The other good news is that post-hoc analysis of the serum potassium changes over time did not show any statistically significant effects of the hormone treatment in two high-risk subsets of subjects, those with renal functional impairment (Cockroft-Gault estimated creatinine clearance of 31 to 80 mL/min), and older women, more than 60 years of age. Also positive is that none of the subjects whose serum potassium exceeded 5.5 mEq/L had any cardiovascular adverse effects or electrocardiographic changes.

However, there are some problems. The fact remains that the incidence of hyperkalemia was almost threefold greater in the hormone-treated group than in the placebo group, although this was not statistically significant. The serum potassium was higher in the hormone group than the placebo group in every week that it was measured, but statistically significant in only 3 of the 11 weeks. We are told that the study was sufficiently powered to show a significant effect of the drug on the number of subjects who attained this end point. The absence of statistical significance may be a function of a smaller-than-required number of subjects, or a smaller-than-anticipated hyperkalemia incidence in both test groups, or the relatively short duration of the study. We will never know.

What are we to make of the percentage of subjects who became hyperkalemic in the three groupings, total (7.3%), diabetic (7.9%), and nondiabetic (6.9%) patients? Are these substantial numbers? What do other studies tell us? It would clearly be foolhardy to compare EPHESUS with the present study, because the patient populations were very different (severe heart failure versus relatively healthy postmenopausal women), different spironolactone analogues were used (epleronone versus drospirenone), and the potassium threshold for “hyperkalemia” was different (≥6.0 mEq/L in EPHESUS v ≥5.5 mEq/L in this study). Nevertheless, the values for hyperkalemia in EPHESUS and the present study were of the same order of magnitude (5.5% and 7.3%). Any reasonable person would happily accept that degree of hyperkalemia risk to achieve EPHESUS-scale improvements in cardiovascular outcomes in postmyocardial infarction patients with terrible left ventricular function. Relatively healthy postmenopausal women are another matter, and our tolerance threshold for potential problems should be very much lower. We should always be super-cautious when considering large-scale interventions in relatively healthy populations using drugs that can be predicted, by their very mode of action, to cause some potentially dangerous side effects.

I really wish that the present study had provided the
cast-iron reassurance that we all need to define with confidence the next candidate for HRT, so that we could proceed to the long-term studies of cardiovascular outcomes that we now know are so essential.

References


